417

418 **Table 3**

419 **Incidence of Adverse Events ≥ 5% of Patients in Clinical Trials (N =**

420 **356)**

421 **(Adverse Events were followed for a period of 12 months following**

422 **RITUXAN therapy.)**

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	**99**	**57**
Body as a Whole	**86**	**10**
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	**25**	**3**
Hypotension	10	1
Hypertension	6	1
Digestive System	**37**	**2**
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	**67**	**48**
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	**38**	**3**
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	**26**	**3**
Myalgia	10	1
Arthralgia	10	1
Nervous System	**32**	**1**
Dizziness	10	1
Anxiety	5	1
Respiratory System	**38**	**4**
Increased Cough	13	1
Rhinitis	12	1

	All Grades (%)	Grade 3 and 4 (%)
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	**44**	**2**
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

Risk Factors Associated with Increased Rates of Adverse Events: Administration of RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[17] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with RITUXAN compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥10 cm) (N = 39) versus patients with lesions < 10 cm (N = 195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

Infusion Reactions (See BOXED WARNINGS and WARNINGS): Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and

hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). In an analysis of data from 356 patients with relapsed or refractory, low-grade NHL who received 4 (N = 319) or 8 (N = 37) weekly infusions of RITUXAN, the incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion).

Infectious Events: RITUXAN induced B-cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4),[17] including sepsis, occurred in 2% of patients.

Hematologic Events: Grade 3 and 4 cytopenias[17] were reported in 12% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia

(2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported. In addition, there have been rare postmarketing reports of prolonged pancytopenia and marrow hypoplasia.

Cardiac Events (See BOXED WARNINGS): Grade 3 or 4 cardiac-related events include hypotension. Rare, fatal cardiac failure with symptomatic onset weeks after RITUXAN has also been reported. Patients who develop clinically significant cardiopulmonary events should have RITUXAN infusion discontinued.

Pulmonary Events (See BOXED WARNINGS): 135 patients (38%) experienced pulmonary events. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. Three pulmonary events have been reported in temporal association with RITUXAN infusion as a single agent: acute bronchospasm, acute pneumonitis presenting 1–4 weeks post-RITUXAN infusion, and bronchiolitis obliterans. One case of bronchiolitis obliterans was associated with progressive pulmonary symptoms and culminated in death several months following the last RITUXAN infusion. The safety of resumption or continued administration

of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immune/Autoimmune Events: Immune/autoimmune events have been reported, including uveitis, optic neuritis in a patient with systemic vasculitis, pleuritis in a patient with a lupus-like syndrome, serum sickness with polyarticular arthritis, and vasculitis with rash.

Less Commonly Observed Events: In clinical trials, < 5% and > 1% of the patients experienced the following events regardless of causality assessment:

agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hyperkinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, weight decrease.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m^2 have been given in controlled clinical trials.[10]

DOSAGE AND ADMINISTRATION

Initial Therapy:

RITUXAN is given at 375 mg/m^2 IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy:

Patients who subsequently develop progressive disease may be safely retreated with RITUXAN 375 mg/m^2 IV infusion once weekly for 4 doses. Currently there are limited data concerning more than 2 courses.

RITUXAN as a Component of Zevalin (Ibritumomab Tiuxetan) Therapeutic Regimen:

As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m^2 should be infused within 4 hours prior to the administration of Indium-111- (In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin. Administration of RITUXAN and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7-9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2–8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNINGS and WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: If the patient tolerated the first infusion well, subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage: RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Refer to the "Preparation and Administration" section for information on the stability and storage of solutions of RITUXAN diluted for infusion.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).

NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).

NDC 50242-053-0

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